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STATE-OF-THE-ART REVIEW

Health Consequences of Environmental Exposures in Early Life: Coping with a Changing World in the Post-MDG Era

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Abstract

Despite overall progress toward achieving the Millennium Development Goals, large health discrepancies persist between developed and developing countries. The world is rapidly changing and the influences of societal change and climate change will disproportionately affect the world's most vulnerable populations, thus exacerbating current inequities. Current development strategies do not adequately address these disproportionate impacts of environmental exposures. The aim of this study was to propose a new framework to address the health consequences of environmental exposures beyond 2015. This framework is transdisciplinary and precautionary. It is based on identifying social and economic determinants of health, strengthening primary health systems, and improving the health of vulnerable populations. It incorporates deliberate plans for assessment and control of avoidable environmental exposures. It sets specific, measurable targets for health and environmental improvement.

KEY WORDS children, noncommunicable disease, social determinants of health, environmental justice, health care systems

INTRODUCTION

The setting of Millennium Development Goals (MDGs) and working toward achieving them has focused a great deal of attention and effort on improving health outcomes for the most vulnerable groups in our population, namely fetuses, young children, and women of childbearing age. In particular, MDGs 4 (reduce child mortality) and 5 (improve maternal health) have resulted in significant advances. Deaths among children age <5 years worldwide have decreased almost 40%,[1] and the number of maternal deaths worldwide declined by 45% from 1990 to 2013.[2] However, for both these

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goals, overall progress obscures the large discrepancies that still exist between developed and developing countries or between communities with different gradients of development within a country. The majority of deaths in children age <5 years occur in low- to middle-income countries, with Africa and Asia bearing a disproportionate burden.[1] These disparities, combined with evidence that exposures during pregnancy or early childhood can set the course for disease or health for the rest of an individual's life, mean that attention to this vulnerable population is needed now more than ever; especially in developing countries.

The vulnerability of pregnant women, the growing fetus, and young children will only increase as changes in environmental exposure patterns occur in the changing world.[3] Climate, economic, and social changes are likely to add to the risks in developed countries. As we move past the MDG era, we propose a plan of action that will:

- Address crucial gaps in knowledge about the lasting effects of early-life environmental stressors;
- Illuminate how consequences of climate change and other shifts in exposures will affect the most vulnerable populations; and
- Advocate for advanced exposure assessment and biomarker development.

Action to reduce avoidable environmental exposures needs to be based on sufficient, but not necessarily definitive, evidence of adverse health consequences for advances to be made in a timely manner.

PRENATAL AND EARLY LIFE: SETTING THE COURSE OF HEALTH FOR A LIFETIME

Evidence abounds that environmental exposures during pregnancy can influence disease risk in children. Diseases that may have at least some origin in exposures that happen during prenatal or early postnatal life were previously reviewed[4] and include asthma, leukemia, obesity, cardiovascular disease, cancer, lowered IQ, autism, schizophrenia, hypertension, and insulin resistance. Maternal intake of a variety of carcinogens and immunotoxicants leads to fetal exposure. For instance, *N*-Nitrosodimethylamine, alcohol, acrylamide, glycidamine, 2-amino-3-methylimidazo [4,5-f] quinoline, and bisphenol A have been shown to have a high rate of transfer via the placenta.[5,6] Exposure to a variety of agents during pregnancy can have toxic effects on children. For instance, maternal diets high in dioxins have been found to contribute to fetal exposure to dioxins and may contribute to reduced birth weight[7] and the effects of prenatal exposure to lead are well documented.

Although some links have been made between exposures to specific chemicals during early life and later disease, as discussed previously,[4] further studies that include a wide range of scientific and biomedical disciplines are required to validate and understand these associations. For example, links between exposures to flame-retardant chemicals and attention deficit-hyperactivity disorder require study in larger populations, especially with detailed exposure assessments and consistent study designs and methods.[8] Associations between early childhood infections and neurodevelopmental diseases must be studied further to elucidate possible explanatory mechanisms.[9] Some authors suggest that understanding the possible link between maternal infection and schizophrenia and autism will best be accomplished by collaborations between geneticists, epidemiologists, and basic and clinical neuroscientists.[10] Because evidence suggests that individual genetic susceptibility can put people at greater risk for disease caused by certain exposures, such as the case with arsenic, large-scale genetic association studies in populations exposed to certain contaminants are needed. However, gene-by-environment interactions also need to be considered when identifying at-risk populations. Ever-improving computational approaches will be required to handle the resulting large datasets.[11] Finally, for diseases such as childhood leukemia, it is important to connect genome-wide association study data about genetic mutations present in those with disease to population-based data about environmental exposures such as diet, chemical exposures, and infections.[12]

A well-recognized example of the long-term effects of an adverse environment during prenatal life is the body of literature supporting the hypothesis that undernutrition during prenatal life can "program" the unborn child's metabolic and endocrine systems to adapt to those conditions; when the nutritional environment in later life differs, the so-called "mismatched" environment, these children can be at increased risk for obesity, diabetes, and heart disease.[11] The most critical window for preventing the long-term effects of malnutrition and undernutrition are during pregnancy and in the first 2 years of a child's life.[13] Lack of specific nutrients in prenatal life or early childhood can exacerbate a variety of diseases and influence long-term health. Other specific examples have been previously discussed.[4]

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CHANGES IN PATTERNS OF ENVIRONMENTAL EXPOSURES: THE EFFECTS OF CLIMATE, ECONOMIC, AND SOCIETAL CHANGES

Changes in patterns of environmental exposures and response to those exposures are expected to occur because of changes in climate, economics, and the social fabric. Figure 1 shows a schematic representation of the effects of climate change on factors likely to have adverse health consequences. Changing weather patterns, increasing drought, and change in land-use patterns are anticipated to decrease water and food security, with the effects likely to be most pronounced in already vulnerable regions. Women and children in low-income, developing countries are already more likely to suffer from chronic malnutrition.[3] Currently, undernutrition is a factor in almost half of all deaths in children age <5 years,[1] and vitamin A deficiency contributes to nearly 800,000 deaths worldwide.[13] Iron deficiency contributes to >18% of total maternal deaths and >23% of perinatal deaths.[13] Climate change is expected to exacerbate these problems, as changes in the nutritional value of food may result as environmental carbon dioxide levels increase; the zinc and iron content of C_3 grains (eg, wheat, rice, barley, oats) and legumes and the protein levels of C_3 crops decrease when grown under field conditions with increased atmospheric carbon dioxide.[14] Food shortage and malnutrition are likely to be exacerbated by crop failure, livestock mortality, and increased grain prices.[3]

Scarcity of food, water shortages, economic change, and sea-level rise in some regions are expected to lead to the emergence of "climate refugees" migrating to other, more fortunate and climate-stable regions. Although climate change and sea-level rise are not recognized under the 1951 Refugee Convention or the 1967 Protocol, the issue is real, especially for the Pacific Island nations. Such population movements have historically changed the distribution of heat-borne, vector-borne tropical diseases.[15] Population migration, together with movement of vectors into areas not previously infested as a result of climate change, is projected to lead to changes in distribution and risk for diseases such as malaria, dengue, and schistosomiasis. For example, increases in mobility among populations and changes in local climate in Brazil and China have led to schistosomiasis exposure in populations previously at little risk.[15] The health consequences of changes in risk for these diseases is uncertain. Effects on maternal health outcome of dengue are not well understood. Although the trend in malaria incidence appears to be decreasing, it is still the cause of as many as 200,000 infant deaths a year in sub-Saharan Africa,[16] and malaria during pregnancy is linked to increased infant mortality risk.[17] The few studies that have assessed the effect of schistosomiasis on pregnancy suggest that it increases risk for anemia in the mother and therefore of low birth weight and maternal mortality; an increased risk for inflammation in the mother, placenta, and the fetus is also expected. Further study is needed to fully characterize the risk posed to mother and fetus by these and other diseases that will be promoted by climate change.[3]

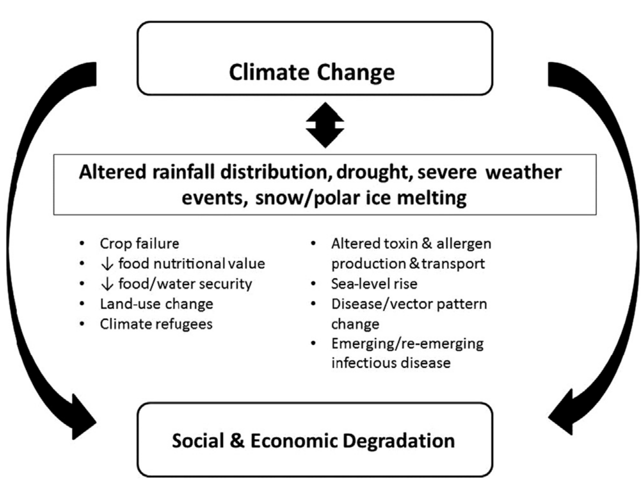

Figure 1. Schematic representation of the climate-sensitive factors likely to adversely affect populations and population health.

Climate change also is expected to alter the transport and toxicity of environmental contaminants and how they enter the human body through inhalation, skin contact, and diet. The nature of these changes will depend on regional conditions and the compound in question. Water alkalinity and temperature have varying effects on toxicity of compounds in water, including pharmaceutical compounds and compound residues.[18] Snow melting, warming temperatures, and the effects on sea ice will all affect release, transport, distribution, and degradation of contaminants.[19,20] These changes are likely to influence the concentrations of a number of compounds in water, air, or sediment; with increasing concentrations for many chemicals. Greater use of pesticides in areas where agriculture increases as a result of changes in rainfall pattern and increased volatilization of pesticides in warmer temperatures may result in new exposures of previously unexposed populations. Additionally, more common and more severe drought will increase the exposure to dust in mining areas located in semi-arid regions; whereas the change in distribution of dengue, malaria, and other transmissible diseases will require the use of pesticides in different locations. Thus, some communities will experience increased exposure to specific toxicants, whereas for others the effect will be just the opposite. Increasing background levels of pesticides in the environment may induce pest resistance to these agents, potentially requiring application of greater amounts or use of more potent alternatives to achieve the same result. The resent reauthorization of the use of DDT to control mosquitos in some malaria-endemic areas is an example of this.

Further research is needed to understand the association between plant nutrient levels and contaminant concentrations and how climate change will affect these relationships, which are likely to be magnified in vulnerable populations, for example, women and children in the Arctic, where reliance on traditional plants, animals, and fish for food are threatened by increasing levels of contaminants, especially organochlorines and heavy metals.[21]

More frequent and more intense storms may lead to increased contaminant spread from runoff. One study found higher concentrations of 6 pesticides in bodies of water in Florida and Oregon when storm intensity increased.[22] Similar increases in pesticide and persistent organic pollutant (POP) contamination of waterways due to increasing storm intensity have been reported elsewhere.[19] Some studies suggest that increased concentrations of POPs and insecticides may weaken the immune system, thereby making people more vulnerable to vector-borne pathogens.

As previously reviewed,[19] many studies indicate that cardiovascular and respiratory diseases are likely to increase in incidence and severity due to hotter temperatures that enhance the toxic effects of ozone and particulate matter. Additionally, increased production of allergens and changes in air pollution may aggravate allergic disease and asthma.[23] Ragweed, common in the United States, has invaded Europe where it is an "invasive alien species." One study predicted a marked increase in the areas of Europe likely to be affected and an increase in airborne pollen concentrations due to climate change and changes in land use in northern and eastern Europe; exposing new populations to this potent allergen.[23] Climate-related changes are predicted to affect the global distribution of nitrogen dioxide, ozone, and particulate matter.[24] Many studies project an overall increase in the degradation of ozone globally because of increased water vapor, leading to an overall decrease in ozone. However, regional pockets with increased levels of ozone are expected to emerge, such as in southern California and in the eastern United States, where increased gas phase reaction rates are expected to be caused by warming temperatures.[24] Dense urban areas are expected to experience greater effects from air pollution. One study using a particular atmospheric chemistry model projected an increase in ozone levels during the summer in New York City and consequently an increase in ozone-related asthma emergency department visits for children age $\leq$17. In central and southern Europe, decreased precipitation is expected to lead to increased ozone levels. Similarly, particular matter concentrations will vary by region and precipitation increase or decrease.[24] Many studies have shown that pollutant concentration may change because of shifts in climate, but much more work is needed to determine how those changes will affect toxicity of those pollutants, as well as human health. There is a need to examine how health in developing countries will be affected as those countries have the most vulnerable populations.[21]

CHANGES IN PATTERNS OF ENVIRONMENTAL EXPOSURES IN RESPONSE TO SOCIETAL CHANGES

Societal changes are sweeping the world, with the pace arguably faster in developing countries. One such change is the increase in the number of children born by cesarean delivery, with an increasing

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number of countries exceeding the rate of 15% considered "reasonable" by the World Health Organization (WHO).[25] Antibiotic use increased by 36% globally between 2000 and 2010 with Brazil, Russia, India, China, and South Africa accounting for 76% of that increase.[26] Antibiotic resistance also is increasing globally.[27] Although cesarean deliveries and antibiotic use are not considered environmental exposures, both can result in changes in the gastrointestinal microbiota, known as dysbiosis, which increases the risk for chronic disease.[28] The infant bowel is sterile at birth and acquires its microbiota by passage through the birth canal, from early feeding patterns, and from the environment. Establishment of the normal gut microbiota can be disrupted by cesarean delivery, premature birth, or increasing use of antibiotics during pregnancy.[28-30] Infants born by cesarean delivery have lower diversity in gut microbiota and a reduction in normal immune responses.[29] Evidence is increasing that the population of gut microbes in each individual are an integral part of the individual's genetic profile and influence risk for disease by playing a key role in stimulation and maturation of the immune system, as well in the biotransformation of environmental xenobiotics.[30,31]

CHILDREN'S ENVIRONMENTAL HEALTH INDICATORS AND SUSTAINABLE DEVELOPMENT

The WHO undertook a pilot project in 2003 to develop and promote a set of children's environmental health indicators (CEHI) that were aimed at improving the assessment, reporting, and monitoring of the effects of interventions to improve children's health in relation to the environment.[32] These indicators were based around 5 main conditions that contributed significantly to childhood disease burden at the time, including perinatal diseases, respiratory diseases, diarrheal diseases, insect-borne diseases, and physical injuries.[33] Each group has exposure and outcome indicators that could be measured at both local and national levels.[32] Given the changes that have occurred in the diseases contributing to the Global Burden of Disease in recent years, these indicators may not be the most appropriate for use in the post-2015 environment. This issue was previously highlighted and demonstrated a discrepancy between the WHO CEHI and the data that are collected and made publicly available in Australia.[34]

To influence policy and inform scientists outside of the field of environmental health, there is a need for better overall assessments of what toxicants children are exposed to, and how much exposure occurs at the local, country, and regional levels. Traditionally, measurements of exposures have been limited to single chemicals, but what is lacking is a good picture of the overall exposure burden for children in specific regions. Also missing is a holistic understanding of which regions have good exposure data available and which lack such data. These issues are highlighted in this edition of *Annals of Global Health*.[35] Using large-scale surveillance programs to take "snapshots" of childhood exposures in various regions will still leave holes in our understanding, but will nevertheless help identify opportunities to better protect children.

One study recently proposed the use of health-related indicators to measure progress in sustainable development in non-health sectors.[36] The proposed indicators reflect the benefits to health outcomes of sustainable development policies, particularly those aimed at reducing greenhouse gas emissions and increasing community resilience to environmental change. The setting of post-2015 sustainable development goals present an opportunity to ensure that health and development outcomes are linked and that health benefits influence global development policies.

A NEW FRAMEWORK TO ADDRESS THE HEALTH CONSEQUENCES OF ENVIRONMENTAL EXPOSURES BEYOND THE MILLENNIUM DEVELOPMENT GOALS

To make progress in understanding and countering the effects of climate, environmental, and societal changes on child health, a number of knowledge gaps need to be filled. To fill these gaps we suggest a framework that accomplishes the areas discussed here (Table 1).

Encourage Transdisciplinary Research. Environmental health scientists must work together with geneticists; basic, clinical, and translational scientists; policymakers; public health risk communication specialists; and others to find the best ways to solve these problems. The effort will require true transdisciplinary research. Researchers and stakeholders from differing disciplines and cultures need to work together to create an entirely new body of knowledge.

Focus on the Most Vulnerable Members of Society. Women of childbearing age, the unborn child, and infants and small children are the most

Table 1. **Elements of a Framework to Address the Health Consequences of Environmental Exposures**

Required Framework Element	Application/Outcomes
Transdisciplinary research	Multiple disciplines will be required to create a new body of knowledge
A focus on vulnerable groups	Include women of childbearing age, the developing fetus, infants, young children, and the elderly
A focus on socioeconomic status, stress, and income disparity	The poor are more vulnerable to climate and social changes
Intervention strategies based on adequate but not necessarily definitive evidence	Reduce avoidable exposures where adverse health consequences are likely
Advanced exposure assessment	Current assessment of exposures during fetal development and early life are inadequate and limit progress
Standardized methods of exposure assessment	Allows combination/comparison of data from different studies
Develop biomarkers of effect and disease	More rapid identification of links between exposure and disease.
Set nation-specific/region-specific targets	Realistic, achievable goals for each locale
Strengthen primary health care systems	Improved ability to cope with unavoidable increases in disease burden

vulnerable to environmental exposures and they will bear the brunt of negative consequences from the anticipated changes in exposures.

Include a Focus on the Role of Socioeconomic Status, Stress, and Income Disparities. Alleviating poverty is an essential part of improving undernutrition and the ability to handle increased risk from climate change.[37] In addition to the previously mentioned vulnerable groups, the poor will be most negatively affected by changes in climate and accompanying upheavals, and they have often been left behind in any gains in mortality rates made because of the MDGs.[21,38]

Encourage Interventions to Reduce Exposures Based on Adequate, but Not Necessarily Definitive, Evidence of Adverse Health Consequences. In many areas we know enough about the health risks associated with exposure to environmental toxicants to act, even if we don't have definitive evidence of causality. For instance, several governments, including those of Canada and the United States, have banned the use of bisphenol A in products designed for use by infants as they felt that the levels of concern were sufficient to take action, although definitive proof was lacking. Other developed countries, including Australia and New Zealand, have not exhibited such forward thinking. At a different level, community-based risk reduction programs should be developed by increasing community capabilities; an example being reducing indoor air pollution by community-based initiatives to replace biomass combustion with cleaner and less harmful fuels.

Apply Advanced Exposure Assessment. Although some early-life exposures, such as to arsenic, have a clear direct link to disease in later life, other exposures, especially those to chemical mixtures, are more difficult to track.[11] Confirmation of early evidence that suggests links between environmental exposures and disease can happen only with biomarkers that can accurately measure exposures, including to mixtures.[39] Additionally, observational studies in humans are limited by the availability of very few longitudinal exposure assessments, so assumptions must be made about how accurately any individual exposure assessment reflects exposure over time. To correct this situation, better biomarkers of exposure are needed. Direct exposure assessment during critical windows will be important, or barring that, improved exposure modeling that does not rely on faulty assumptions. For example, measuring maternal level of chemicals in blood or serum is not a good proxy for measuring newborn exposure, in part because it does not account for exposure via breastfeeding, which makes up the bulk of exposure for newborns, and also because maternal levels can fluctuate widely throughout pregnancy.[40]

Standardize Models of Exposure Assessment. Combining data from pregnancy and birth cohort studies may be helpful to ensure sample sizes that are sufficiently large, especially for rare diseases.[11] However, in assessing exposure to chemicals during prenatal and early postnatal life, cohort studies have not been consistent in the type of biological specimen measured; in whom it is measured (mother, father, or offspring); the type of analysis conducted; and the time windows during prenatal and postnatal life in which exposure is assessed. Instituting standardized measurement methods, time windows for measurement, validation, and harmonization of measurement tools

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would be ideal, but will require extensive coordination and collaboration between key research groups and areas.

Develops Biomarkers of Effect and Disease. Epigenetic markers such as DNA methylation have the potential to identify people at increased risk for later disease, possibly presenting an opportunity for early intervention even after exposures have occurred. It remains to be seen whether these markers can reveal mechanisms and suggest ways to intervene at the mechanistic level. Other questions for further research include whether nonepigenetic mechanisms exist by which early-life events contribute to disease many years later, whether those events can be tracked through early markers, and how they are affected by sex differences. Answering those questions will involve basic biological research to better understand disease mechanisms and how genetic and epigenetic perturbations may lead to disease.[11] Biomarkers that have shown promise but that require further confirmation include chromosomal translocations originating in utero and disease-related patterns of DNA methylation.[11]

Sets Nation-specific or Region-specific Targets. Progress on the MDGs has varied widely across countries. One shared goal to reduce child mortality or improve maternal health may be too general to foster real progress.[41] This is not surprising because, for many low-income countries, the goals were too ambitious, whereas for middle-income countries, they were very easy to meet. For example, some countries, including some in Asia and Latin America, added extra or set higher targets when they were easy to reach.[42]

Strengthens Primary Health Care Systems as Well as Focuses on Specific Exposures or Diseases. Policymakers increasingly recognize the importance of strong primary health care systems in targeting specific diseases and implementing programs focused on specific diseases.[43] Many researchers have pointed out the crucial need for strong general health care systems in neutralizing the extra burden that climate change will place on vulnerable populations, especially women and children, through essential services such as improved health care during pregnancy, education of women of childbearing age,[3] vaccination and well child care, and family planning to reduce population growth and improve maternal health.[38] For this objective to be achieved, a different type of health care professional, one with a wider perspective of the relations between environment and health, is likely to be required.

CONCLUSION

Although progress toward meeting the MDGs is undeniable and welcome, disparities between developed and developing countries are hidden within the statistics. The rapidly changing world with a changing climate, rapid urbanization, and changing socioeconomic conditions pose new challenges as we enter the beyond-2015 era. New thinking and a willingness to tackle global public health challenges in a new way is required. We propose a new approach to tackle the continuing global challenges with the aim of reducing avoidable environmental exposures and improving global health.

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